REMARKS

These remarks are responsive to the Office Action mailed March 30, 2010 ("Office Action"). Applicants gratefully acknowledge the Examiner's indication that claims 29, 35 and 40 would be allowable if rewritten in independent form. Applicants respectfully request that the rejections of the remaining claims be reconsidered and withdrawn for the following reasons.

Amendments to the claims

Claims 9-11, 17, 28-30, and 32 are amended in response to an objection. Because this amendment complies with a requirement of form expressly set forth in the Office Action, its entry after a Final Rejection is proper. See MPEP 714.12 and 37 C.F.R. § 1.116(b)(1).

Claims 12, 33, 38, and 44 are cancelled herewith, without disclaimer of subject matter, to place the application in better condition for appeal. Since this amendment does not affect the scope of the pending claims, its entry after a Final Rejection is proper. See MPEP 714.12 and 37 C.F.R. § 1.116(b)(1).

No new matter is added by these amendments. These amendments are made solely to advance the prosecution of this application and without any disclaimer of subject matter. Applicants continue to reserve the right to pursue any cancelled subject matter in a continuing or divisional application.

Claim objections

Claims 9-12, 17, 28-29, and 32 were newly objected to. Specifically, the Office Action states that "in order to improve claim form and consistency and because a majority of the dependent claims recite 'The method', it is suggested that 'A method' be amended to recite 'the method'." Office Action, page 3. Though this objection appears to be based solely on a stylistic preference rather than any *bona fide* requirement for patentability, nonetheless to advance prosecution the remaining claims are amended as the Examiner has suggested (except for claim 12 which is cancelled herewith, rendering the objection moot as to this claim).

Definiteness and nonstatutory subject matter

Claim 44 was newly rejected as allegedly indefinite for claiming a use of a culture as obtained in the method of claim 1 without setting forth steps involved in the method/process. For similar reasons, claim 44 was also rejected as allegedly directed to non-statutory subject matter. However, when read in light of the specification, one of skill in the art would understand the steps involved in the method. Nonetheless, to advance prosecution, claim 44 is cancelled herewith, without disclaimer of subject matter, rendering the rejection moot.

New matter

Claim 12 was rejected as allegedly containing new matter for the recitation of a plasmid including a DNA sequence encoding an ATPase. Specifically, the Examiner contends that the disclosure does not support this sub-genus of the genetically modified strains recited in the application. However, Applicants respectfully submit that the rejection overlooks that the original disclosure includes that which is implicitly disclosed. A person of ordinary skill in the art would readily understand plasmids including a DNA sequence encoding an ATPase to be among the genera disclosed in the specification, for example in page 11, line 26 to page 12, line 9. Nonetheless, to advance prosecution, claim 12 is cancelled herewith, without disclaimer of subject matter, rendering the rejection moot.

Rejections under 35 U.S.C. § 102/103

Applicants gratefully acknowledge the withdrawal of the prior rejections under 35 U.S.C. § 102/103 over Dickely et al. (US Patent 5,691,185; cited as reference A in the Form PTO-892 mailed on 3/27/02; hereafter "Dickely") as evidenced by Groboillot et al. (*Biotechnol. Bioengineer.* 42:1157-1163, 1993; hereafter "Groboillot") and over Dickely as evidenced by Luksas (US Patent 3,720,520; hereafter "Luksas").

Rejections under 35 U.S.C. § 103

The claims at issue relate to methods for fermentation and acidification of milk and other substrates using non-proliferating bacterial strains. The specification describes that conventional

proliferating bacterial cultures are susceptible to bacteriophage attack which can cause fermentation failure. *See* Specification, pg. 1. The specification also states that known methods to address this problem (such as use of mixed bacterial cultures and rotation of bacterial strains) do not provide reliable protection and have other shortcomings. *See* Specification, pg. 3. The present specification teaches methods of using non-proliferating bacterial strains for fermentation of milk and other substrates, and that these bacterial strains are not susceptible to bacteriophage attack. Working examples demonstrate that these methods can successfully ferment milk even when high concentrations of bacteriophages are deliberately added to the culture. *See* Specification, Examples 1 and 2 (particularly pages 17-18 and 21-22).

In contrast to the present claims, the cited references each only concern uses of proliferating bacterial cultures. Only one reference that discloses the existence of any non-proliferating strain, specifically a *pur-* strain, but that reference only teaches making that strain Pur+ (by adding an appropriate plasmid) and using the resulting Pur+ strain for fermentation.

For these reasons, and the further deficiencies of the rejections that are described below, Applicants respectfully traverse and request reconsideration and withdrawal of the rejections.

A. Claims 1, 9-10, 17, 24, 30, 31, 33, 37, and 43-44

Claims 1, 9-10, 17, 24, 30, 33, 37, and 43-44 have been rejected as allegedly obvious over Dickely as evidenced by Luksas. Because the Office Action also includes a quotation from claim 31 in this section, Applicants understand the rejection to have been intended to be applied to this claim and its dependent claim 38 as well. It is undisputed that Dickely only teaches that a purine auxotrophic bacterial strain can not grow in milk. It is also undisputed that none of the cited references disclose or suggest that a purine auxotrophic bacterial strain could ferment milk despite its inability to replicate in milk. Nonetheless, the rejection is based on the allegation that one of ordinary skill in the art would have been motivated to culture a purine auxotrophic strain in milk in order to verify that a suspected purine auxotrophic strain was in fact a purine auxotroph. Moreover, the rejection is based on the position that the claims do require any acidification or fermentation of milk to occur, or in the alternative that fermentation and

acidification occur whenever as few as two individual organic molecules are broken down into an acidic product. Applicants respectfully traverse.

The rejections are based on an unreasonable interpretation of the claims. Claim 1 provides "[a] method of fermenting milk comprising adding a cultured purine or thymidine auxotrophic bacterial strain to milk and *keeping the milk under conditions where the bacterial culture is able to acidify the milk*, wherein said auxotrophic bacterial strain is non-proliferating in the milk" (emphasis added). The rejection is based on the Examiner's interpretation of the italicized phrase. The Examiner takes the position that acidification need not occur even though the milk is kept "under conditions where the bacterial culture is able to acidify the milk." The Examiner states that this phrase relates to the culture conditions rather than the result achieved. However, the claim sets forth sufficient conditions for acidification to occur, namely the adding of bacteria to milk and keeping the milk under conditions where the bacterial culture is able to acidify the milk. It is tautological that acidification results when the milk is kept under conditions where the bacterial culture is able to acidify the milk. Accordingly, it is unreasonable to interpret the claimed method to lack any acidification. Since this unreasonable interpretation formed the basis of the rejection, the rejection is improper.

The rejections of the remaining claims share the same underlying defect. Though the language of independent claims 1, 30, and 31 differ, each recites a method that includes adding bacteria to a substrate and keeping that substrate under conditions where acidification or fermentation of that substrate occurs. Thus, in each instance, the claims set forth sufficient conditions for acidification or fermentation to occur. Since each rejection was based on a contrary and unreasonable interpretation of the claims, the rejections are improper.

As an alternative interpretation of the claims, the Examiner alleges that if fermentation or acidification are part of the claimed method, then breakdown of as few as two individual organic molecules would suffice. The alleged justification for this interpretation is the statement in the specification that fermentation "relates to any aerobic or anaerobic breakdown of organic compounds by a bacterial culture with the production of an end product." Specification, pg. 6, lines 4-5 (emphasis added). Since the plural term "compounds" is listed, the Examiner interprets fermentation to mean breakdown of two or more individual organic molecules (*i.e.*, breakdown

involving just one organic molecule would not meet this definition). The Examiner then provides an interpretation of the term acidification that is "[i]n line with this definition [of fermentation]" to require only the breakdown of two organic molecules to yield acidic products. Office Action, page 11. Based on these interpretations, the Examiner concludes that fermentation and acidification occur with any addition of metabolically active bacteria to milk. Applicants respectfully submit that these interpretations are also unreasonable and unjustified. Under the purported interpretation, if even a single living bacterium is added to milk for a brief instant (long enough for chemical reactions to break down *two* organic molecules into acidic products), then fermentation and acidification have occurred. Indeed, even if a single bacterium were broken open and its cytoplasm dumped into an ocean of milk, the last dying gasp of its metabolic machinery would presumably be sufficient for fermentation and acidification of that milk in the Examiner's view, even though that milk might appear completely unchanged by even the most sensitive of detection method. This interpretation defies common sense and is inconsistent with the way those terms are used in the art (*see, e.g.*, first paragraph of Dickely) and in the specification. For example, the specification describes the problem of "fermentation failure" resulting when bacteria are added to milk but are then killed by bacteriophages. Specification, pg. 3. Since bacteria remain metabolically active for some time after infection (during which the normal metabolic machinery are co-opted for production of more bacteriophages) it is clear that "fermentation" as the Examiner has defined it would still occur, yet the specification describes this as "fermentation failure." Similarly, the specification describes working examples in which the ability of bacterial strains to achieve "acidification" is determined by measuring changes in the pH of the milk (not by detecting whether a few individual organic molecules are broken down). *See, e.g.*, Example 1 (particularly page 17 and Fig. 1), and Example 2 (particularly page 21 and Fig. 4). Thus, the Examiner's interpretations of the claim terminology is contradictory to the usage of these terms in the art and in the specification.

The purported interpretation of the term "fermentation" is based solely on a statement in the specification that fermentation "*relates to*" -- not "is defined as" -- "any aerobic or anaerobic breakdown of organic compounds by a bacterial culture with the production of an end product." In this context, the phrase "relates to" simply means "involves," and accordingly the Examiner's

interpretation lacks any legitimate basis. Additionally, the sole stated rationale for the purported interpretation of the term "acidification" is conformity with the Examiner's interpretation of the term "fermentation." Even if there were some reason that the definitions of "acidification" and "fermentation" should be preferred to conform to one another (and no such reason has been given), the purported definition of "fermentation" is improper and accordingly a definition of "acidification" to conform to this definition is likewise improper.

The aforementioned claim interpretations that form the basis of the rejection are further inconsistent with the language of each claim when read as a whole. Claim 1 recites "[a] method of fermenting milk," claim 30 recites a "method for keeping the capability of a bacterial strain to ferment milk," and claim 31 recites "[a] method of preparing a dairy flavouring and/or a product for cheese flavouring." None of these results could be achieved unless acidification or fermentation occurred, thus, the Examiner's interpretation of the claims as lacking acidification or fermentation is inconsistent with each claim when each is read as a whole, and therefore the interpretations are unreasonable for this further reason.

Additionally, no valid motivation is given for the Examiner's proposed modification of the reference disclosure. The primary reference, Dickely, is cited for its statement that a purine auxotrophic strain of *L. lactis* was unable to grow in milk. This statement provides the sole purported motivation for one of ordinary skill in the art to have practiced the claimed method. Specifically, the Office Action alleges that one of ordinary skill in the art would have been motivated to culture purine auxotrophic bacterial strains in milk in order to select purine auxotrophic strains and to verify that a bacterial strain was in fact a purine auxotroph. However, as to the alleged motivation of "selection," the Office Action does not elaborate on how milk could be used for selection of a purine auxotrophic strain. It is possible that the intention was that milk containing an antibiotic might be used for selection of non-growing strains which would be purine auxotrophs, however, the art of Dickely teaches using a medium completely free of purines that is made by treating a defined medium to remove residual purines (specifically, by boiling the medium with activated charcoal). Dickely, pg. 845, left column (describing methods of making media free of residual purines), and pg. 842, left column (describing culturing in purine-free media containing ampicillin to enrich for purine auxotrophic strains). The Office

Action does not provide any evidence of methods for eliminating residual purines from milk that would result in a usable growth medium. Moreover, there is no justification given for one of skill in the art to attempt to develop such a medium rather than simply use the medium described in Dickely). Additionally, the Office Action does not provide any explanation of why one of ordinary skill in the art would choose to verify purine auxotrophy by attempting to grow a strain in milk rather than use of conventional methods of testing auxotrophy, *i.e.*, use of the aforementioned defined purine-free medium as taught by Dickely. Indeed, Dickely uses defined purine-free media, rather than milk, for selection and verification of purine auxotrophy. See pg. 842, left col. Contrary to the alleged basis of rejection, the art of Dickely only teaches using milk as a selective medium such that an otherwise *pur-* strain will retain a suppressor plasmid that renders the strain Pur+. Thus, Dickely only teaches culturing a Pur+ bacterial strain in milk and does not provide any legitimate justification for attempting to culture a purine auxotrophic strain in milk.

Moreover, as stated above, the present methods include conditions sufficient for fermentation or acidification of milk. Even if a purine auxotrophic strain were inoculated into milk to test its growth ability (which Dickely does not justify), there is no stated justification to have cultured under the conditions sufficient for acidification or fermentation to occur. The Office Action and cited references do not provide any reason for one to have used a sufficient inoculum or sufficient culture duration to have achieved acidification or fermentation. Rather, one of ordinary skill in the art would prefer to use a very low inoculum to test growth ability to ensure that any observed growth was not simply due to background growth which may result from residual purines contained in the medium or carried over in the inoculum, and further to minimize the possibility of a spontaneous revertant that could grow in the medium and confound the test results (the higher the inoculum, the more likely that a spontaneous revertant would be present). See, e.g., Dickely, pg. 842, right col. (spontaneous Pur+ revertants arose with a frequency of approximately 1 per 10^6 viable cells). Thus, in addition to failing to provide any legitimate justification for culturing a purine auxotrophic strain in milk, the Office Action also does not provide any reason to have used a sufficient inoculum for acidification or fermentation to occur (and indeed, general scientific principles indicate a preference a low inoculum to minimize the appearance of background growth).

The secondary reference, Luksas, is only cited for the proposition that milk is considered to be a product for cheese flavoring as recited in claim 31. Office Action, page 8. Luksas is not alleged to (and does not) remedy any of the foregoing deficiencies of Dickely (or indeed have any stated application against any of the claims other than claim 31 and its dependents).

Thus, contrary to the alleged basis of rejection, the claims do include steps sufficient for fermentation or acidification of the culture. Further, the purported definitions of "fermentation" and "acidification" to only require reaction of a few individual molecules have no legitimate basis and are contrary to the usage of these terms in the specification and in the art. Moreover, the Office Action does not articulate any reason why one of ordinary skill in the art would have chosen to isolate verify purine auxotrophy by culturing strains in milk rather than by using conventional purine-deficient media (as exemplified in Dickely), and even if milk were utilized there is no justification to have used culture conditions that would result in acidification or fermentation as recited in the claims. Rather, whatever the culture medium, Dickely teaches a strong preference to use a low inoculum due to the high frequency of Pur+ revertants, and there is no evidence that such a low inoculum would have inherently resulted in acidification or fermentation. Thus, the Office Action does not articulate a proper prima facie case of obviousness.

B. Claims 11, 34, 36, 39, and 41-42

Claims 11, 34, 36, 39, and 41-42 have been rejected as allegedly obvious over Dickely as evidenced by Luksas and in further view of Barach *et al.*, US Patent 4,294,930 (hereinafter, Barach) as evidenced by Groboillot *et al.*, *Biotechnol. Bioengineer.* 42:1157–1163 (1993) (hereinafter, Groboillot). Applicants respectfully traverse.

The deficiencies of the teachings of Dickely and Luksas are addressed in the preceding section. Barach and Groboillot are not alleged to, and do not, remedy any of these deficiencies. Accordingly, claims 11, 34, 36, 39, and 41-42, each of which properly depend from claim 1 or 31, are not obvious for at least the reasons stated above with those claims.

Further, as to claims 11 and 42, Barach is alleged to teach that "when culturing a microbe in milk, it is desirable to use 10^8 CFU/mL." The sole purported justification for the proposed

combination of references is as follows: "[o]ne would have been motivated to use 10^8 CFU/mL of the culture of the [purine auxotrophic] strain because Barach teaches this is desirable." Office Action, page 13. However, Barach only teaches that this inoculum is "desirable" when culturing a proliferating strain in order to make a "fermented food product." Barach, col. 1, line 6. In contrast, Dickely teaches that a purine auxotrophic strain is non-proliferating and does not disclose or suggest that such a strain could be used to generate a fermented food product. Indeed, the sole supposed justification for culturing a purine auxotrophic strain in milk is to select for a purine auxotrophic strain and verify its inability to grow, Barach does not teach any inoculum for such uses. There is no evidence to suggest that one of ordinary skill in the art would use a relatively high inoculum used in making fermented food products (as taught by Barach) when choosing an inoculum to test growth ability. Rather, as discussed above, general scientific principles indicate that a low inoculum would be preferred, for example to minimize background growth and the confounding effects of spontaneous revertants. As discussed above, Dickely teaches that spontaneous Pur+ revertants arose with a frequency of approximately 1 in 10^6 viable cells and thus one of ordinary skill in the art would have used a much lower inoculum to avoid spontaneous revertants which would confound growth test results. Accordingly, there is no legitimate justification for the proposed combination of reference teachings; rather, the art teaches away from this combination. Therefore, the references do not provide (and the Examiner has not identified) any valid motivation to inoculate 10^8 CFU/mL of a non-replicating *pur*$^-$ strain into milk.

Additionally, as to claims 34 and 39, the purported motivation for culturing the bacterium in a medium comprising a purine is "in order to achieve 10^8 CFU/mL of the culture for growth analysis" as allegedly taught by Barach. However, as stated above with claims 11 and 42, Barach does not provide any valid justification for using this inoculum to use for growth analysis, and thus for this further reason the Office Action has not stated a valid *prima facie* case of obviousness against these claims.

As to claims 36 and 41, the Examiner has taken the position that acidification to pH less than or equal to 5.0 would be the inherent result of inoculating a *pur*- bacterium into milk to test growth ability. The alleged evidence for this position is a truncated quotation from the

discussion in the present specification. Additionally, a secondary reference, Groboillot, is cited for evidence that a proliferating strain of *L. lactis* has a doubling time of about 1 hour when grown in milk, and thus if a growth test is conducted for about 100 generation times, this would correspond to a culture time of about 100 hours. However, the quoted portion of the specification teaches that this degree of acidification is only achieved with a sufficient inoculum. For example, Figure 1 shows that the rate of acidification depends on inoculum, and that acidification to pH less than 5.5 was only achieved with the highest inoculums tested under these conditions. In this figure, percentages referred to dilution of an outgrown culture, *i.e.*, 50% means an outgrown culture was washed and resuspended in twice its original volume. Acidification to pH less than 5.5 was only observed with the highest inoculums tested (50% and 25%) and not with 10% or 1% inoculums. Even if one of ordinary skill in the art were to use milk as a medium to test growth ability (which is unjustified for the reasons stated above), there is no reason given to use such a high inoculum. Rather, as discussed above, general scientific principles teach a preference for using a lower inoculum to minimize background growth and the possible confounding effect of spontaneous revertants. Indeed, one of ordinary skill in the art would have used a much lower inoculum because Dickely teaches that spontaneous Pur+ revertants arose with a frequency of approximately 1 in 10^6 viable cells. Due to the exponential nature of bacterial growth an inoculum as small 0.0001% or even lower would be sufficient to test for growth ability, yet there is no evidence to suggest that such a minimal inoculum could acidify milk to the recited pH within the contemplated time-frame (100 hours in the Examiner's proposed modification of the references). Accordingly, acidification to pH less than or equal to 5.0, as recited in the claims, would not be the inherent result of the Examiner's proposed modification of the reference disclosure.

C. Claim 28

Claim 28 has been rejected as allegedly obvious over Dickely as evidenced by Luksas as applied to claims 1, 9-10, 17, 24, 30, 33, 37, and 43 above and in further view of Nilsson et al. (*Mol. Gen. Genet.* 235:359-364, 1992; hereafter "Nilsson"). However, whatever bacterial strains are taught by Nilsson, the reference fails to remedy any of the aforementioned deficiencies of

Dickely and Luksas, and accordingly claim 28 is not obvious over these references for at least the reasons stated above with claim 1 (from which claim 28 depends).

D. Claim 32

Claim 28 has been rejected as allegedly obvious over Dickely as evidenced by Luksas as applied to claims 1, 9-10, 17, 24, 30, 33, 37, and 43 above and in further view of Jochimsen *et al.* (*Mol. Gen. Genet.*, 143:85-91, 1975; hereafter "Jochimsen"). However, whatever purine auxotrophic bacterial species are taught by Jochimsen, the reference fails to remedy any of the aforementioned deficiencies of Dickely and Luksas, and accordingly claim 28 is not obvious over these references for at least the reasons stated above with claim 1 (from which claim 28 depends).

CONCLUSION

Applicants submit that this amendment addresses all of the issues raised in prior Office Actions and places all claim in condition for allowance. An early notice to that effect is respectfully solicited. The Examiner is invited to contact the undersigned directly at (703) 714-7645 if it would be helpful for resolution of any remaining issues.

It is respectfully submitted that no fee is required for entry of this amendment and consideration of this application. However, in the event any fees are deemed necessary, the Commissioner is authorized to charge such fees to the undersigned's Deposit Account No. **50-0206**.

Respectfully submitted,
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Dated: 6/30/10

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